

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Robert M. Townsend et al. Examiner: Phillip Gambel, Ph.D.
Serial No.: 09/877,987 Group Art Unit: 1645
Filed: June 8, 2001 Docket: D0009NP; 30436.53USDA
Title: METHODS FOR REGULATING A CELL-MEDIATED IMMUNE RESPONSE BY
BLOCKING LYMPHOCYTIC SIGNALS AND BY BLOCKING LFA-1-MEDIATED
ADHESION

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By: 
Name: Tracy Truick

55 South Lake Avenue, Suite 710
Pasadena, California 91101
January 14, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

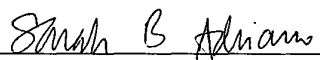
Sir:

We are transmitting herewith the attached:

- ☒ Transmittal Sheet in duplicate containing Certificate under 37 C.F.R. 1.8
- ☒ Supplemental Information Disclosure Statement (37 C.F.R. §1.97(b))
- ☒ Form 1449 (Information Disclosure Statement)
- ☒ Exhibits 88-189
- ☒ Return postcard

Please charge any and/or additional fees or credit overpayment to Deposit Account No. 50-0306. A duplicate of this sheet is enclosed.

MANDEL & ADRIANO
55 South Lake Avenue, Suite 710
Pasadena, California 91101
(626)395-7801

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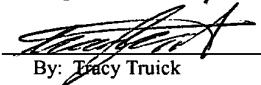


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Robert M. Townsend, et al. **Examiner:** Phillip Gambel, Ph.D.
Serial No.: 09/877,987 **Group Art Unit:** 1644
Filed: June 8, 2001 **Docket No.:** D0009NP/30436.53USU1
Title: METHODS FOR REGULATING A CELL-MEDIATED IMMUNE RESPONSE
BY BLOCKING LYMPHOCYTIC SIGNALS AND BY BLOCKING LFA-1
MEDIATED ADHESION

CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on January 14, 2003.


By: Tracy Truick

55 South Lake Avenue
Suite 710
Pasadena, California 91101
January 14, 2003

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b) 3))

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This Information Disclosure Statement is being filed herewith as a supplement to Applicant's October 26, 2001, Information Disclosure Statement which was submitted under 37 C.F.R. § 1.97 (b) before the mailing date of the first Office Action on the merits. In accordance with 37 C.F.R. § 1.98(d), copies of Exhibits 88-189 as set forth in the Form 1449 are included herewith.

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- Linsley, et al., 1991, *J.Exp.Med.* "CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" 174:561-569. (Exhibit 88)

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- Gimmi, et al., 1993, *Proc.Natl.Acad.Sci. USA* "Human T-Cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" 90:6586-6590. **(Exhibit 89)**
- Azuma et al., 1993 *Nature* "B70 antigen is a second ligand for CTLA-4 and CD28" 366:76-79. **(Exhibit 90)**
- Ronchese et al., 1994 *J.Exp.Med* "Mice Transgenic for a Soluble Form of Murine CTLA-4 Show Enhanced Expansion of Antigen-specific CD4 T Cells and Defective Antibody production In Vivo" 179:809-817. **(Exhibit 91)**
- Griggs et al., 1996 *J.Exp.Med* "The Relative Contribution of the CD28 and gp39 Costimulatory pathways in the Clonal Expansion and Pathgenic Acquisition of Self-reactive T Cells" 183:801-810. **(Exhibit 92)**
- Verwilghen et al., 1994 *J-Immunol.* Expression of Functional B& and CTLA4 on Rheumatoid Synovial T Cells" 153:1378-1385. **(Exhibit 93)**
- Blazar et al., 1994 *Blood* "In Vivo Blockade of CD28/CTLA4: Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatibility Complex Barrier in Mice" 83:3815-3825. **(Exhibit 94)**
- Finck et al., *Science* "Treatment of Murine lupus with CTLA4Ig" 265:1225-1227. **(Exhibit 95)**
- Perrin et al., 1995 *J-Immunol* "Role of B7:CD28/CTLA4 in the Induction of Chronic Relapsing Experimental Allergic Encephalomyelitis" 154:1481-1490. **(Exhibit 96)**
- Pearson et al., 1994 *Transplantation* "Transplantation Tolerance Induced By CTLA4-Ig" 57:1701-1706. **(Exhibit 97)**
- Baliga et al., 1994 *Transplantation* "CTLA4Ig PROLONGS ALLOGRAFT SURVIVAL WHILE SUPPRESSING CELL-MEDIATED IMMUNITY" 58:1082-1090. **(Exhibit 98)**
- Tepper et al., 1994 *Transplantation Proceedings* "Tolerance Induction by soluble CTLA4 in a Mouse Skin Transplant Model" 26:3151-3154. **(Exhibit 99)**

- Perico et al., 1995 *Kidney International* "Toward novel antirejection strategies: In vivo immunosuppressive properties of CTLA4Ig" 47:241-246. **(Exhibit 100)**
- Finck et al., 1994 *Arthritis and Rheumatism* "Effects of CTLA4Ig in murine lupus" 37:S222. **(Exhibit 101)**
- Nishikawa et al., 1994 *Eur J. Immunol.* "Effect of CTLA-4 chimeric protein on rat autoimmune anti-glomerular basement membrane glomerulonephritis" 24:1249-1254. **(Exhibit 102)**
- Wallace et al., 1994 *Transplantation* "CTLA4ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers" 58:602-610. **(Exhibit 103)**
- Damle et al., *J. Immunol.* "Costimulation of T Lymphocytes with integrin Ligands intercellular Adhesion Molecule-1 or Vascular Cell Adhesion Molecule-1 Induces Functional Expression of CTLA-4, a Second Receptor for B7" 152:2686-2697. **(Exhibit 104)**
- Milich, et al., 1994 *J. Immunol* "Soluble CTLA-4 can suppress autoantibody production and elicit long term unresponsiveness in a novel transgenic model," 153:429-435. **(Exhibit 105)**
- Webb, et al., 1996 *Eur J. Immunol* "Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2," 26:2320-2328. **(Exhibit 106)**
- Van Oosterhout, et al., 1997 *Am.J.Respir.Cell Mol.Biol.* "Murine CTLA4-IgG Treatment Inhibits Airway Eosinophilia and Hyperresponsiveness and Attenuates IgE Upregulation in a Murine Model of allergic Asthma," 17:386-392. **(Exhibit 107)**
- Abrams et al., 1999 *J-Clin-Invest* "CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. 103:1243-1252. **(Exhibit 108)**
- Ibrahim, et al., 1996 *Blood* "CTLA4Ig Inhibits Alloantibody Responses to Repeated Blood Transfusions," 88:4594-4600. **(Exhibit 109)**

- Lenschow, et al., 1995 *J Exp Med* "Differential Effects of anti-B7-1 and Anti-b&-2 Monoclonal Antibody Treatment on the Development of Diabetes in the Nonobese Diabetic Mouse," 181:1145-1155. **(Exhibit 110)**
- Lenschow, et al., 1992 *Science* "Long-Term Survival of Xenogeneic Pancreatic islet Grafts Induced by CTLA4Ig," 257:789-792. **(Exhibit 111)**
- Sayegh., 1999 *J Clin Invest* "Finally, CTLA4Ig graduates to the clinic," 103:1223-1225. **(Exhibit 112)**
- Wolfe, 1995 *Bailliere's Clinical Rheumatology* "The epidemiology of drug treatment failure in rheumatoid arthritis," 9:619-632. **(Exhibit 113)**
- Hochberg, et al., 1990 *Epidemiologic Reviews* "Epidemiology of Rheumatoid Arthritis: Update," 12:247-252. **(Exhibit 114)**
- Spector, 1990 *Epidemiology of Rheumatic Disease* "Rheumatoid Arthritis," 16:513-537. **(Exhibit 115)**
- Liu MF, Kohsaka H Sakurai H, Azuma m Okumura K Saito I, Miyasaka N, 1996. "The presence of costimulatory molecules B7.1 (CD80) and B7.2 (CD86) in rheumatoid arthritis synovium" *Arthritis-Rheum.* Jan; 39(1): 110-4. **(Exhibit 116)**
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- Parkin D, Jacoby A, McNamee P, 2000. "Treatment of multiple sclerosis with interferon β : an appraisal of cost-effectiveness and quality of life" *J Neurol Neurosurg Psychiatry*; 68: 144-149. **(Exhibit 120)**

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- Pearson TC, Alexander DZ, Winn KJ, Linsley PS, Lowry RP, Larsen CP, 1994. "Transplantation tolerance induced by CTLA4-Ig. *Transplantation*, 57:1701-1706.
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- Liao HX, Haynes BF, 1995. "Role of adhesion molecules in the pathogenesis of rheumatoid arthritis" *Rheum-Dis-Clin-Noth-Am.* Aug; 21(3): 715-40. **(Exhibit 123)**
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- Schiff M, 1997. "Emerging treatments for rheumatoid arthritis" *Am-J-Med.* Jan 27; 102 (1A): 11S-15S **(Exhibit 127)**
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- Aruffo, S., March 27, 2000, Presentation of “Approaches to Immune Regulation” at BIO 2000 in Boston, Mass. **(Exhibit 132)**
- Abrams, et al., September 4, 2000, *J.Exp.Med.* “Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte- associated Antigen 4-Immunoglobulin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells,” 192:681-693. **(Exhibit 133)**
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- Gandhi, et al., November 18, 1998, Abstract and Presentation of *PharmSci Supplement* “Physical and Chemical Characterization of BMS-224818, A Recombinant Fusion Protein,” in San Francisco, Ca. **(Exhibit 135)**
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- Srinivas, N.R., April 8, 1997, *Pharmaceutical Research* “Assessment of Dose Proportionality, Absolute Bioavailability, and Immunogenicity Response of CTLA4Ig

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- Weiner, R.S., June 6, 1996, *J Pharmaceutical and Biomedical Analysis* “A sensitive enzyme immunoassay for the quantitation of human CTLA4Ig fusion protien in mouse serum: pharmacokinetic application to optimizing cell line selection,” 15:571-579. **(Exhibit 140)**
- Warner, G.I. et al., March 16-22, 1995, Abstract and Presentation of “Bioactivity of BMS-188667 (CTLA4Ig) in Cynomolgus Monkeys,” in Seattle, Washington. **(Exhibit 141)**
- Weiner, R.S., March 1, 2000, Abstract and Presentation of “Industrial Perspectives of Primary Analytical Tools for Macromaloecules- Principles and Applications with Examples.” **(Exhibit 142)**
- Weiner, R.S., November 1995 Abstract and Presentation of “Validation of an Enzyme Immunoassay For The Quantition of Human CTLA4Ig Fusion Protein In Human Serum,” in Miami, Florida. **(Exhibit 143)**
- Weiner, R.S., November 1995 Abstract and Presentation of “Automation and Validation of An EIA For Quantition of Human CTLA4Ig In Monkey Serum,” in Miami, Florida. **(Exhibit 144)**
- Webb, L.M.C. et al., July 23, 1996 *Eur J Immunol* “Prevention and amelioration of collagen-induced arthritis by blockade of the CE28 co-stimulatory pathway: requirement for both B7-1 and B7-2” 26:2320-2328. **(Exhibit 145)**
- Knoerzer, et al., May 5, 1995, *J Clin. Invest* “Collagen-induced Arthritis in the BB Rat Prevention of Disease by Treatment with CTLA4Ig” 96:987-993. **(Exhibit 146)**

- Larsen, et al., April 27, 2000, Abstract of "Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-Ig Fusion Protein In Non-Human Primates," in *Transplantation*, 69(8): #44, p. S123, Chicago, Il. **(Exhibit 147)**
- Larsen, et al., May 13-17, 2000, A Presentation of "Prolongation of Renal Allograft Survival With Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-Ig Protein In Nonhuman Primates" at the American Society of Transplantation Meeting in Chicago, Il. **(Exhibit 148)**
- Larsen, Aug. 27-Sept.1, 2000, A Presentation of "Manipulation of Costimulatory Pathways: Targeting CD80 and CD86" at the XVII congress of the Transplantation Society in Rome, Italy. **(Exhibit 149)**
- Larsen, March 3-4, 2000, A Presentation of "Costimulation blockade: progress toward clinical application" at Canadian Society of Transplantation Annual Scientific meeting in Mont Tremblant, Quebec, Canada. **(Exhibit 150)**
- Larsen, Jan. 13-17, 2000, A Presentation of "Costimulation blockade: Progress toward clinical application" at the American Society of Transplantation Meeting in Las Croabas, Puerto Rico. **(Exhibit 151)**
- Hathcock, et al., August 30, 1993 *Science* "Identification of an Alternative CTLA-4 Ligand Costimulatory for t Cell Activation," 262:905-911. **(Exhibit 152)**
- Sfrikakis, et al., November 29, 1994 *Arthritis & Rheumatism* "CD28 Expression On T Cell Subsets in Vivo And CD28-Mediated T Cell Response In Vitro In Patients With Rheumatoid Arthritis," 38:649-654. **(Exhibit 153)**
- U.S. Patent No. 5,434,131, July 18, 1995. **(Exhibit 154)**
- PCT No. WO 02/02638 A2, January 10, 2002. **(Exhibit 155)**
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- Pearson, Thomas C., et al., "TRANSPLANTATION TOLERANCE INDUCED BY CTLA4-Ig¹," *Transplantation*, 1994, 57:1701-1706. **(Exhibit 158)**
- Alexander, Diane Z., "ANALYSIS OF A FUNCTIONAL ROLE FOR CHIMERISM IN CTLA4-Ig PLUS BONE MARROW-TREATED CARDIAC ALLOGRAFT RECIPIENTS," *Transplantation*, 1994, 91:416-418. **(Exhibit 159)**
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- Pearson, Thomas C., et al., "CTLA4-Ig PLUS BONE MARROW INDUCES LONG-TERM ALLOGRAFT SURVIVAL AND DONOR-SPECIFIC UNRESONSIVENESS IN THE MURINE MODEL", *Transplantation*, 1996, 61:997-1004. **(Exhibit 161)**
- Weber, C.J., et al., "CTLA4-Ig Prolongs Survival of Microencapsulated Rabbit Islet Xenografts in Spontaneously Diabetic Nod Mice," *Transplantation Proceedings*, 1996, 28:821-823. **(Exhibit 162)**
- Alexander, D.Z., et al., "Analysis of effector mechanisms in murine cardiac allograft rejection," *Transplantation Immunology*, 1996, 4:46-48. **(Exhibit 163)**
- Larsen, Christian P., et al., "Long-Term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways," *Nature*, 1996, 381:434-438. **(Exhibit 164)**
- Elwood, Eric T., et al., "Microchimerism and rejection in clinical transplantation," *The Lancet*, 1997, 349:1358-1360. **(Exhibit 165)**
- Larsen, Christian P., and Thomas C. Pearson., "The CD40 pathway in allograft rejection, acceptance, and tolerance," *Transplantation*, 1997, 9:641-647. **(Exhibit 166)**
- Konieczny, Bogumila T., et al., "IFN- γ Critical for Long-Term Allograft Survival Induced by Blocking the CD28 and CD40 Ligand T Cell Constimulation Pathways¹," *The Journal of Immunology*, 1998, 160:2059-2064. **(Exhibit 167)**

- Elwood, Eric T., et al., "PROLONGED ACCEPTANCE OF CONCORDANT AND DISCORDANT XENOGRAFTS WITH COMBINED CD40 AND CD28 PATHWAY BLOCKADE¹," *Transplantation*, 1998,65:1422-1428. **(Exhibit 168)**
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- Bingaman, Adam W., et al., "Vigorous Allograft Rejection in the Absence of Danger¹," *Journal of Immunology*, 2000,164:3065-3071. **(Exhibit 171)**
- Bingaman, Adam W., et al., "TRANSPLANTATION OF THE BONE MARROW MICROENVIRONMENT LEADS TO HEMATOPOIETIC CHIMERISM WITHOUT CYTOREDUCTIVE CONDITIONING," *Transplantation*, 2000, 69:2491-2496. **(Exhibit 172)**
- Durham, Megan M., et al., "Cutting Edge: Administration of Anti-CD40 Ligand and Donor Bone Marrow Leads to Hemopoietic Chimerism and Donor-Specific Tolerance Without Cyto-reductive Conditioning¹," *Cutting Edge*, 2000, 165:1-4. **(Exhibit 173)**
- Williams, Matthew A., et al., "Genetic Characterization of Strain Differences in the Ability to Mediate CD40/CD28-Independent Rejection of Skin Allografts¹," *The Journal of Immunology*, 2000, 165: 6549-6857. **(Exhibit 174)**
- Bingaman, Adam W., et al., "The role of CD40L in T cell-dependent nitric oxide production by murine macrophages," *Transplant Immunology*, 2000, 8:195-202. **(Exhibit 175)**
- Adams, Andrew B., et al., "Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct

Genetic Hemoglobinopathies with Minimal Myelosuppression¹,” *The Journal of Immunology*, 2001, 167:1103-1111. **(Exhibit 176)**

- Meng, L., “Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection,” *Transplantation Proceedings*, 2001, 33:418-420. **(Exhibit 177)**
- Guo, Zhong., et al., “CD8 T CELL-MEDIATED REJECTION OF INTESTINAL ALLOGRAFTS IS RESISTANT TO INHIBITION OF THE CD40/CD154 COSTIMULATORY PATHWAY,” *Transplantation*, 2001, 71:1351-1354. **(Exhibit 178)**
- Ha, Jongwon., et al., “Aggressive skin allograft rejection in CD28^{-/-} mice independent of the CD40/CD40L costimulatory pathway,” *Transplant Immunology*, 2001, 9:13-17. **(Exhibit 179)**
- Bingaman, Adam W., et al., “ANALYSIS OF THE CD40 AND CD28 PATHWAYS ON ALLOIMMUNE RESPONSES BY CD4⁺ T CELLS IN VIVO¹,” *Transplantation*, 2001, 72:1286-1292. **(Exhibit 180)**
- Adams, Andrew B., et al., “Calcineurin Inhibitor- Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates,” *Diabetes*, 2002, 51:265-270. **(Exhibit 181)**
- Whelchel, JD., et al. “Evolving Strategies in immunosuppressive Therapy: The Emory Experience,” *Clinical Transplants*, 1996, 20:249-255 **(Exhibit 182)**
- Ritichie, SC., et al., “Regulation of Immunostimulatory function and B7 molecule expression on murine dendritic cells,” *Journal of Cellular Biochemistry*, 1995, 21A:C1-215 **(Exhibit 183)**
- Alexander, DZ., et al., “Analysis of the mechanisms of CTLA4-Ig plus bone marrow induced transplantation tolerance,” *Journal of Cellular Biochemistry*, 1995, 21A:C1-301 **(Exhibit 184)**

- Alexander, DZ., et al., "CTLA4-Ig induced transplantation tolerance: analysis of donor cell chimerism," Surgical Forum, 1994, 45:402-403 (**Exhibit 185**)
- Pearson, TC., et al., "CTLA4-Ig plus bone marrow induces transplantation tolerance in the murine model," Journal of Cellular Biochemistry, 1995, 21A:C1-327 (**Exhibit 186**)
- Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," Journal of the American Society of Nephrology, 1996, 7:A3204 (**Exhibit 187**)
- L104EA29Y (Figure 6, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
- L104EA29Y (Figure 6 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.
 - L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
 - L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
- A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 188**.
 - The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R. §20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation

and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.

- The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
- The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 188), which differs from CTLA4Ig at two amino acid residues, Leu₁₀₄-Glu and Ala₂₉-Tyr (Exhibit 188 at page 2).
- An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 189**.
 - The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
 - The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
 - The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 189), but not the sequence of L104EA29Y (Figure 6, of the subject application).

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the references are not "prior art." Applicants wish to reiterate that the documents and information above were not at the time of filing publicly available since they were provided under confidentiality agreements.

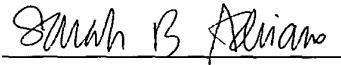
Consideration of the items listed is respectfully requested. Applicants invite the Patent Office to request additional information if necessary. Pursuant to the provisions of M.P.E.P. 609, it is

Robert Townsend, et al.
Serial No. 09/877,987
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Page 14

Consideration of the items listed is respectfully requested. Applicants invite the Patent Office to request additional information if necessary. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,

A handwritten signature in cursive script, reading "Sarah B. Adriano", is written over a horizontal line.

Sarah B. Adriano
Registration No. 34,470
Attorney for Applicants
Mandel & Adriano
55 South Lake Avenue, Suite 710
Pasadena, California 91101
(626) 395-7801
Customer No. 26,941

FORM 1449*

**INFORMATION DISCLOSURE STATEMENT
IN AN APPLICATION**

(Use several sheets if necessary)

Docket Number

D0009NP;30436.53USU1

Application Number

09/877,987

Applicant

Robert M. Townsend et al.

Filing Date

June 8, 2001

Group Art Unit

1645

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLAS S	FILING DATE IF APPROPRIATE
	5,434,131 (Exhibit 154)	7/18/95	Linsley et al.			5/26/93

FOREIGN PATENT DOCUMENTS

DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLAS S	TRANSLATION	
					YES	NO
WO 95/33770 (Exhibit 124)	12/14/95	PCT				X
WO 02/02638 A2 (Exhibit 155)	1/10/02	PCT				X

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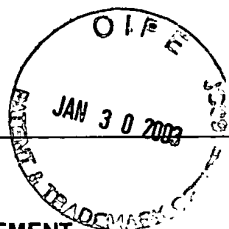
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	D0009NP;30436.53USU1	09/877,987
	Applicant	
	Robert M. Townsend et al.	
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		Wallace et al., 1994 <i>Transplantation</i> "CTLA4Ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers" 58:602-610. (Exhibit 103)
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	Applicant Robert M. Townsend et al.	
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FORM 1449*

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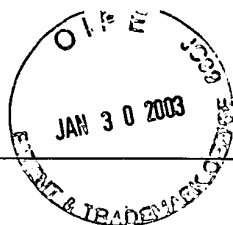
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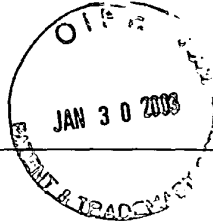
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		Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," <i>Journal of the American Society of Nephrology</i> , 1996, 7:A3204 (Exhibit 187)
		L104EA29Y (Figure 6, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
		L104EA29Y (Figure 6 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.

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		L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
		L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
		A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as Exhibit 188 .
		The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R. §20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
		The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
		The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 171), which differs from CTLA4Ig at two amino acid residues, Leu104-Glu and Ala29-Tyr (Exhibit 171 at page 2).
		An Investigator Brochure dated January 26, 1999 is enclosed as Exhibit 189 .
		The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
		The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
		The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 172), but not the sequence of L104EA29Y (Figure 6, of the subject application).

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	